Amendments to the Specification:

Please amend the title as follows:

~~REMEDY FOR INTERNAL ADMINISTRATION AGAINST CRANIAL NERVE DISEASES CONTAINING MESENCHYMAL CELLS AS THE ACTIVE INGREDIENT~~

<u>INTERNALLY ADMINISTERED THERAPEUTIC AGENTS FOR CRANIAL NERVE DISEASES COMPRISING MESENCHYMAL CELLS AS AN ACTIVE INGREDIENT</u>

Please amend the specification as follows:

Page 5, beginning at line 30, please replace the paragraph with the following rewritten paragraph:

Herein the term "mesenchymal cells" preferably refers to, for example, bone marrow cells (mononuclear cell fraction of bone marrow cells; MCF (~~mononuclera~~ <u>mononuclear</u> cell fraction)), cord blood cells, peripheral blood cells, mesenchymal stem cells (MSCs), or cells derived from these cells. The mesenchymal cells of the present invention include, for example, mesenchyme-related cells, mesoblastic stem cells, and so on. Even if cells referred to as "mesenchymal cells" in the present invention are classified as cells other than mesenchymal cells in the future, the cells can still be suitably used in the present invention.

Please replace the paragraph bridging pages 12 & 13 with the following rewritten paragraph:

The present inventors have also found that MSCs introduced with genes other than the BDNF gene, such as the GDNF (glial cell line-derived neurotrophic factor), CNTF (~~cliary~~ <u>ciliary</u> neurotrophic factor), or NT3 (neurotrophin-3) gene, show therapeutic effects on cerebral infarction. They have verified that mesenchymal stem cells introduced with IL-2 gene have therapeutic effects on a rat brain tumor model. Thus, preferred embodiments of the mesenchymal cells for use in the present invention are mesenchymal cells introduced with the BDNF gene, PLGF gene, GDNF gene, or the IL-2 gene. Specifically, mesenchymal cells with an exogenous BDNF gene, PLGF gene, GDNF gene, or IL-2 gene in an expressible condition are preferably used as mesenchymal cells in the present invention.

Please replace the paragraph bridging pages 21 & 22 with the following rewritten paragraph:

FIG. 5 shows photographs depicting the result of intravenously administering autologous MCFs ($1x10^7$ cells) to a rat cerebral infarction model, in which A shows transplanted ~~MCFG cells~~ <u>MCF cells</u> (blue) accumulating in a cerebral infarction area. B is a photograph obtained by high power magnification of the region indicated by

the open square in A (HE staining). C is a visualized image of the same region as in B (in blue) after treatment with x-gal; many transplanted MCF cells (blue) have accumulated; LacZ-positive cells (D) are found to be NSE-positive (E), and F is a merged view of D and E; LacZ-positive cells (G) are found to be GFAP-positive (H), and I is a merged view of G and H.

Page 24, beginning at line 26, please replace the paragraph with the following rewritten paragraph:

FIG. 29A is a ~~photograph~~ graph of T2-weighted images (T2W) of rats administered with DMEM, fibroblasts, MSCs, or MSC-BDNF taken two, seven, and 14 days after MCAO. Seven days after MCAO, the MSC-BDNF-treated rats showed a significant reduction in HLV (%) as compared to rats treated with DMEM (P=0.002), fibroblasts (P=0.015), or MSCs (P=0.028). Fourteen days after MCAO, the MSC-BDNF-treated rats showed a significant reduction in HLV (%) compared with the DMEM-treated rats (P=0.011).

Page 25, beginning at line 22, please replace the paragraph with the following rewritten paragraph:

FIGS. 33a to 33e are ~~photographs~~ graphs showing the expression of surface antigens in rat MSCs analyzed by flow cytometry. The MSCs were labeled with monoclonal antibodies specific to the antigen to be presented. Dead cells were removed by front and side scattering. FIGS. 33f to 33i are photographs indicating the differentiation of rat MSCs into typical mesenchymal cells. Osteogenic differentiation of primary MSCs or MSC-IL2s was detected by von Kossa staining. Adipogenic differentiation of primary MSCs (h) or MSC-IL2s (i) was detected by Oil Red O staining.

Page 29, beginning at line 32, please replace the paragraph with the following rewritten paragraph:

LacZ gene was introduced into the bone marrow cells (~~mononuclera~~ mononuclear cell fraction: MCF) before transplantation to the rat cerebral infarction model (transient middle cerebral artery occlusion model).

Page 32, beginning at line 14, please replace the paragraph with the following rewritten paragraph:

Using the same infarction parameters, the bone marrow cells were intravenously administered 3, 6, 12, 24 and 72 hours after infarct induction. At all these time points the transplantations reduced the infarct volume, but better results were obtained when transplantation was conducted in the early stages after ischemia induction. When the autologous bone marrow cells were intravenously administered three hours after MCAO, virtually no infarct was detected (FIG. 3A); changes in TTC staining were barely detected, but a slight inflammatory response was detected in the target infarcted lesion. When the cells were administered six hours after MCAO, the intensity of TTC staining was reduced in the infarct at the basal ganglia (40 ± 28 mm^3, n=6)

(FIG. 3B). The infarct gradually increased when the cells were administered 12 hours (80±25 mm^3, n=6, FIG. 3C), 24 hours (140±18 mm^3, n=6, FIG. 3D), and 72 hours (180±22 mm^3, n=6, ~~FIG. 1E~~ FIG. 3E) after MCAO.

Page 33, line 22, please replace the paragraph with the following rewritten paragraph:

The transplanted ~~MCFG cells~~ MCF cells were treated with X-gal to visualize the donor cells in blue.

Page 36, beginning at line 6, please replace the paragraph with the following rewritten paragraph:

[Example 11] Therapeutic effects of using mesenchymal stem cells

The intravenous administration of bone marrow cells (~~mononuclera~~ mononuclear cell fraction: MCF) exhibited significant therapeutic effects on cerebral infarction. Mesenchymal stem cells (MSCs), which exist in about 0.1% of MCF, were also used for treatment and their therapeutic effects were confirmed. Mesenchymal stem cells can be easily sampled, cultivated, proliferated, and preserved.

Page 45, beginning at line 40, please replace the paragraph with the following rewritten paragraph:

After confirming the induction of ischemic brain injury using the behavioral tests described below, the animals were randomized for transplantation. The animals were anaesthetized with intraperitoneal (IP) injection of ketamine (2.7 to 3 mg/100-g) and xylazine (0.36 to 0.4 mg/100-g) and positioned in a Narishige stereotaxic frame (Model SR-6N, Narishige Co., Ltd., Japan). Using a 26-gauge Hamilton syringe, 5 μl of a suspension of 5x 10^5 MSCs in serum-free DMEM was injected to the right dorsolateral striatum 4 mm beneath the skull surface and ~~3 m~~ 3 mm lateral to the bregma level over 2.5 minutes (Paxinos, G., Watson, C., Pennisi, M. and Topple, A. (1985). Bregma, lambda and the interaural midpoint in stereotaxic surgery with rats of different sex, strain and weight. J Neurosci Methods 13, 139-143.). This position was approximately the ischemic boundary zone. To prevent rejection of human MSCs transplants, the transplanted rats were intraperitoneally administered with cyclosporine A (10 mg/kg/day).

Page 50, beginning at line 3, please replace the paragraph with the following rewritten paragraph:

A large number of DsR-positive MCS cells were detected less than 2 mm from the injection site. The ~~MSC-BENF-treated~~ MSC BDNF-treated animals showed a reduced number of TUNEL-positive transplanted MSCs in the injection site, as compared to the MSC group (FIG. 31D). In addition, compared to the MSC group, the MSC-BDNF-treated animals showed a reduced number of TUNEL-positive cells near MSCs in the injection site[,].

Page 53, beginning at line 35, please replace the paragraph with the following rewritten paragraph:

It is unclear whether or not *in vivo* administration of MSCs to brain tumors affects tumor growth. However, MSCs are known to produce cytokines such as fibroblast growth factor ~~(GFG)~~ (FGF), and other tumor growth factors (TGFs) capable of supporting tumor growth (Tille JC, Pepper MS. Mesenchymal cells potentiate vascular endothelial growth factor-induced angiogenesis *in vitro*. Exp Cell Res 2002; 280: 179-191.). The present inventors initially evaluated the effects of MSC co-culture on the growth of 9L glioma cells *in vitro*.

Page 59, beginning at line 31, please replace the paragraph with the following rewritten paragraph:

Genes other than the BDNF (brain-derived neurotrophic factor) gene, such as GDNF (glial cell line-derived neurotrophic factor), CNTF (~~cliary~~ ciliary neurotrophic factor), or NT3 (neurotrophin-3) gene, were introduced into MSCs, and production of BDNF, GDNF, CNTF and NT3 by cultivated cells was examined.

Page 60, beginning at line 8, please replace the paragraph with the following rewritten paragraph:

For CNTF, MSCs transfected with AxCAhCNT-F/RGD (MSC-CNTFs) at MOIs of 300, 1000, or ~~300~~ 3000 pu/cell secreted CNTF at rates of 0.136 ± 0.028, 0.854 ± 0.145, and 3.58 ± 0.43 ng/10^5 cell/48-hr, respectively. Untransfected MSCs also produced CNTF protein (0.0520 ± 0.0150 ng/10^5 cell/48-hr).